Case reports

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Hyperosmolar hyperglycaemic non-ketotic diabetic coma complicating open heart surgery

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A 53-year-old woman developed hyperosmolar non-ketotic diabetic coma after open heart surgery. The operation, and various drugs given after operation, may have precipitated the disorder. There was delay in diagnosis and the institution of appropriate therapy with a fatal outcome.

The syndrome of hyperosmolar hyperglycaemic non-ketotic diabetic coma was first described by Sament and Schwartz in 1957. In a recent publication, McCurdy (1970) reviewed the details of 84 cases. Various possible aetiological factors have been considered, and in an Editorial in *Journal of the American Medical Association* (1968), attention was drawn to an iatrogenic element. It has complicated peritoneal dialysis (Boyer, 1967), anterior pituitary stalk resection (Kolodny and Sherman, 1968), corticosteroids (Spenney, Eure, and Kreisberg, 1969), diphenylhydantoin therapy (Goldberg and Sanbar, 1969), and cerebral compression (Davidson, 1970).

This report describes a patient developing the syndrome after open heart operation and special emphasis is placed on the role of medical management in its causation.

Case report

A 53-year-old housewife was found to have post-rheumatic mitral stenosis – regurgitation and aortic regurgitation in November 1967. Cardiac catheterization confirmed this diagnosis and the pulmonary artery pressure was 60/25 mmHg, with an end-diastolic gradient of 10 mmHg across the mitral valve. She had suffered *grand mal* seizures at the age of 19 years for which she had received anticonvulsants over a period of 6 years.

She was readmitted in October 1969, for open heart surgery, while on digoxin, 0·25 mg daily, chlorthalidone 100 mg on alternate days, potassium supplements, and warfarin. Her urine was free from sugar.

On 28 October 1969, the mitral valve was replaced by a size 3 Starr Edwards prosthesis and the aortic valve by a size 8 Starr Edwards valve using normothermic cardiopulmonary bypass. (Dextrose was not used to prime the heart lung machine.) The patient was fully conscious at the end of the operation.

The next morning she was drowsy and confused. The only localizing sign was a right-sided grasp reflex. Multiple ventricular extrasystoles were only partially controlled during the next 24 hours with five intravenous injections of 250 mg diphenylhydantoin. On the second postoperative day, digoxin was started together with frusemide 40 mg and Slow-K 1200 mg twice daily.

She had a major epileptiform convulsion starting on the left side, which progressed to status epilepticus despite treatment with phenobarbitone and diazepam. Curarization and intermittent positive pressure ventilation with tracheostomy were necessary to control the fits. In addition, she received hydrocortisone 100 mg 6-hourly intravenously to reduce presumed cerebral oedema. Cardiac action was stable at this time and the urine output adequate (100 ml/hr). Serum electrolytes, urea, calcium, and magnesium were all normal. Urine examination revealed glycosuria without ketonuria.

There was little change in her condition over the next 48 hours until she developed a right upper lobe pneumonia. When *Klebsiella pneumoniae* was cultured, antibiotic therapy was changed from ampicillin to kanamycin. Several episodes of hypotension and tachycardia were thought to be due to ventilator difficulties. Coma persisted.

On the sixth postoperative day her level of consciousness improved slightly, but neurological examination revealed bilateral pyramidal signs

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and nystagmus to the left. Further episodes of peripheral circulatory failure were treated with isoprenaline infusion and dextran.

On the 10th postoperative day, she became deeply unconscious and unresponsive. Investigations revealed blood sugar 744 mg/100 ml; blood urea 300 mg/100 ml; serum sodium 158 mEq/l., potassium 6·2 mEq/l., chloride 124 mEq/l., *p*H 7·22; standard bicarbonate 13·5 mEq/l., P_{CO_2} 31·5 mmHg, P_{O_2} 78 mmHg, base deficit 13 mEq/l., Hb 17·0 g/100 ml, PCV 54 per cent. Serum acetone nil. Estimated plasma osmolarity 370 mOsm/l. (Effective plasma osmolarity estimated from blood glucose, sodium, and potassium levels.)

She was given 340 units of intravenous soluble insulin over the next 5 hours, and fluid replacement with hypotonic saline and potassium was initiated. Six hours later the blood sugar had fallen to 250 mg/100 ml without improvement in her cerebral state. Death followed a cardiac arrest 17 hours after therapy had been started.

At necropsy the heart weighed 650 g and both prosthetic valves were securely seated. There was an extensive right upper lobe bronchopneumonia. The brain was congested but no infarction was detected. The kidneys, suprarenals, and pancreas were all normal, and there was no evidence of thromboembolism.

Discussion

The average age of patients developing hyperosmolar hyperglycaemic non-ketotic diabetic coma is 57 years (McCurdy, 1970), and two-thirds, like the patient under review, have no previous history of diabetes mellitus.

In more than half the cases, there is a precipitating event such as infection, burns, pancreatitis, or the ingestion of drugs known to aggravate diabetic control.

In our patient, several factors may have contributed to the development of her hyperosmolar state. It has been shown (Allison, Prowse, and Chamberlain, 1967) that there is a failure of insulin response to injected glucose during operation, and Clarke (1970) has shown that postoperative hyperglycaemia is proportional to the stress of operation. We have seen glycosuria in other open heart surgical cases, some of which had hyperglycaemia (J. B. Meade, W. A. Littler, and C. C. Evans, 1970, unpublished observations). This is thought to be due to suppression of insulin secretion (Majid *et al.*, 1969).

Dollery, Pentecost, and Samaan (1962) showed that thiazide diuretics could induce diabetes mellitus, and in 1963 Cranston and his colleagues reported the death of a previously non-diabetic man with probable hyperglycaemic hyperosmolar coma after chlorthalidone therapy. In 1966, the diabetogenic effect of frusemide was described by Toivonen and Mustala. Our patient received chlorthalidone 300 mg weekly for two years before operation and frusemide 40 mg daily after operation (Table).

TABLE *Dosage of drugs with possible aetiological significance*

Drug	*Dose (mg)*	*Total dosage*	*Administration*	*Time of administration*
Chlorthalidone	100	30 g	Orally	Preop.
Diphenylhydantoin	250	1·25 g	Intravenously	Postop.
Frusemide	40	280 mg	Intravenously	Postop.
Hydrocortisone	100	4·0 g	Intravenously	Postop.

Two other drugs known to have produced hyperosmolar diabetic states were also used. Four grammes of hydrocortisone were given postoperatively over a 10-day period for presumed cerebral oedema. Spenney *et al.* (1969) have reported cases in which corticosteroids were thought to have precipitated the condition. They added two of their own cases where prednisolone and azathioprine together apparently did so. Diphenylhydantoin can induce hyperglycaemia in animals and humans, and Goldberg and Sanbar (1969) have reported a case of hyperosmolar hyperglycaemic non-ketotic diabetic coma in which this drug was thought to have contributed. Our patient received large concentrations of this preparation 25 mg/kg for 36 hours, in a fruitless attempt to control ventricular arrhythmias which later responded to intravenous potassium chloride.

These four drugs are commonly used, often in combination, in patients undergoing heart operations, and it is essential that blood sugar estimations are performed whenever glycosuria is detected.

If there is delay in diagnosis, the glycosuria and its attendant osmotic diuresis lead to dehydration, peripheral circulatory failure, coma, and death. In these patients, who do not develop ketosis, the pre-coma phase is often much longer than is usual in patients developing ketoacidotic diabetic coma. Neurological features include tremor, muscle fasciculations (Jackson and Forman, 1966), epileptic convulsions, and focal signs (Maccario, Messis, and Vastola, 1965). These signs occur after open heart surgery in patients with neurological damage (Javid *et al.*, 1969), especially those on intermittent positive pressure ventilation receiving muscle relaxants.

The laboratory diagnosis rests on profound glycosuria without acetonuria, and extreme hyperglycaemia without ketoacidosis. Hyperosmolarity is frequent but not essential. If raised postoperative electrolyte and haemoglo in levels are detected, hyperosmolarity

must be considered and a search made for glycosuria.

More than 5 l. fluid are usually required during the first 12 hours of therapy and hypotonic saline is recommended. This is essential, since the administration of water in 5 per cent dextrose leads to perpetuation of the osmotic diuresis and therefore worsens dehydration. Insulin needs are unpredictable. They tend to be less than in ketoacidotic coma. Clements, Prockop, and Winegrad (1968) believed that a speedy reduction of the blood sugar level might lead to cerebral oedema aggravating the neurological status. Though biochemical improvement was achieved in this case, she remained deeply unconscious and died 17 hours after therapy was started.

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